

CLAIMS

1. A method for treating a Pin1-associated state in a subject comprising administering to a subject an effective amount of a fredericamycin A compound such that the Pin1-associated state is treated.
2. The method of claim 1, wherein the Pin1-associated state is a cyclin D1 elevated state.
3. The method of claim 1, wherein the Pin1-associated state is neoplastic transformation.
4. The method of claim 1, wherein the Pin1-associated state is cancer.
5. The method of claim 1, wherein the Pin1-associated state is tumor growth.
6. The method of claim 1, wherein the treating comprises inhibiting tumor growth.
7. The method of claim 1, wherein the treating comprises preventing the occurrence of tumor growth in the subject.
8. The method of claim 1, wherein the treating comprises reducing the growth of a pre-existing tumor in the subject.
9. The method of claim 1, wherein the Pin1-associated state is colon cancer.
10. The method of claim 1, wherein the Pin1-associated state is breast cancer.
11. The method of claim 1, wherein the Pin1-associated state is a sarcoma.
12. The method of claim 1, wherein the Pin1-associated state is a malignant lymphoma.
13. The method of claim 1, wherein the Pin1-associated state is esophageal cancer.

14. The method of claim 1, wherein the Pin1-associated state is caused by overexpression of Pin1.

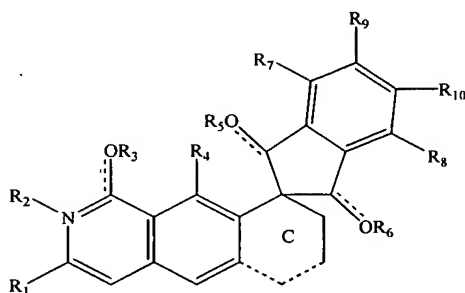
5 15. The method of claim 1, wherein the Pin1-associated state is caused by DNA damage.

16. The method of claim 1, wherein the Pin1-associated state is caused by an oncogenic protein.

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17. The method of claim 1, wherein the Pin1-associated state is caused by Ha-Ras.

18. The method of claim 1, wherein the fredericamycin A compound has  
15 Formula IX

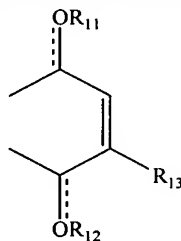


wherein the dotted lines around C indicate that C may be a 5 or 6 membered ring;  
wherein the dotted lines not around C indicate optional double bonds;

R<sub>1</sub> is alkyl, alkenyl, alkanoyl, alknyl;

20 R<sub>2</sub> is hydrogen or alkyl;

R<sub>9</sub> and R<sub>10</sub> are both hydrogen or together form a ring having the structure



R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>11</sub>, and R<sub>12</sub> are independently hydrogen, alkyl, alkanoyl, or nothing; and R<sub>4</sub>,  
R<sub>7</sub>, R<sub>8</sub>, R<sub>13</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl,  
25 alkoxycarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, or  
pharmaceutically acceptable salts, ester, or prodrugs thereof.

19. The method of claim 1, wherein the fredericamycin A compound is



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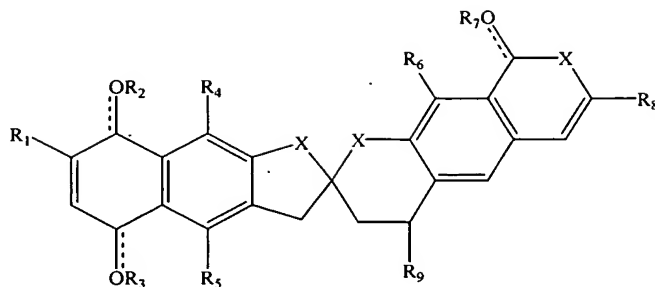
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1, VV





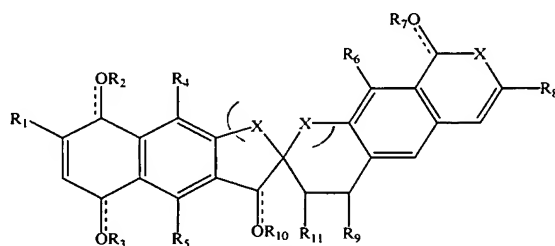
wherein the dotted lines indicate optional double bonds;

X is N, O, S, or C;

R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, and R<sub>9</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxy carbonyl, alkyl carbonyl, alkyl carbonyloxy, alkoxy carbonyloxy; and

R<sub>2</sub>, R<sub>3</sub>, and R<sub>7</sub> are independently hydrogen, alkyl, alkanoyl, or nothing, or pharmaceutically acceptable salts, ester, or prodrugs thereof.

23. The method of claim 1, wherein the fredericamycin A compound has Formula XI



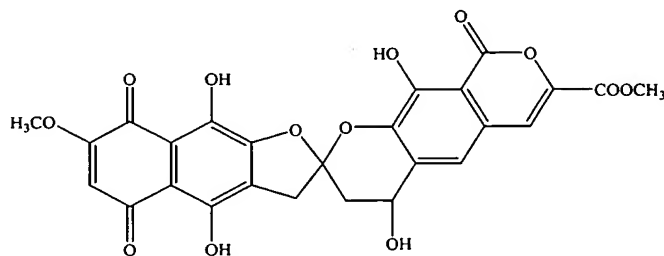
wherein the dotted lines indicate optional double bonds;

X is N, O, S, or C;

R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>11</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxy carbonyl, alkyl carbonyl, alkyl carbonyloxy, or alkoxy carbonyloxy, or R<sub>9</sub> and R<sub>11</sub> taken together form an epoxide ring; and

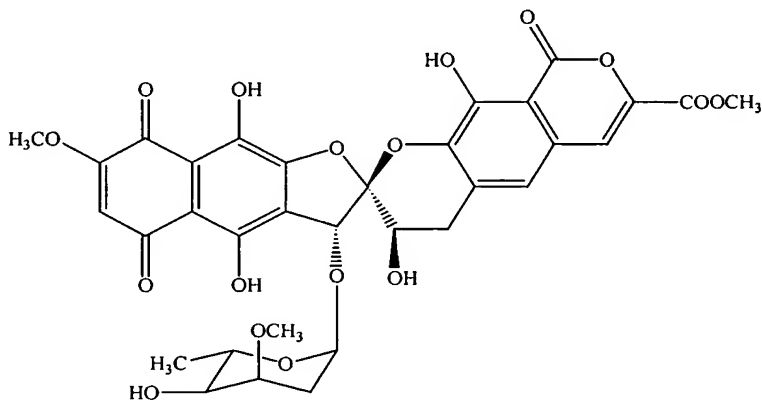
R<sub>2</sub>, R<sub>3</sub>, R<sub>7</sub>, and R<sub>10</sub> are independently hydrogen, alkyl, alkanoyl, or nothing, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

24. The method of claim 1, wherein the fredericamycin A compound has Formula VII



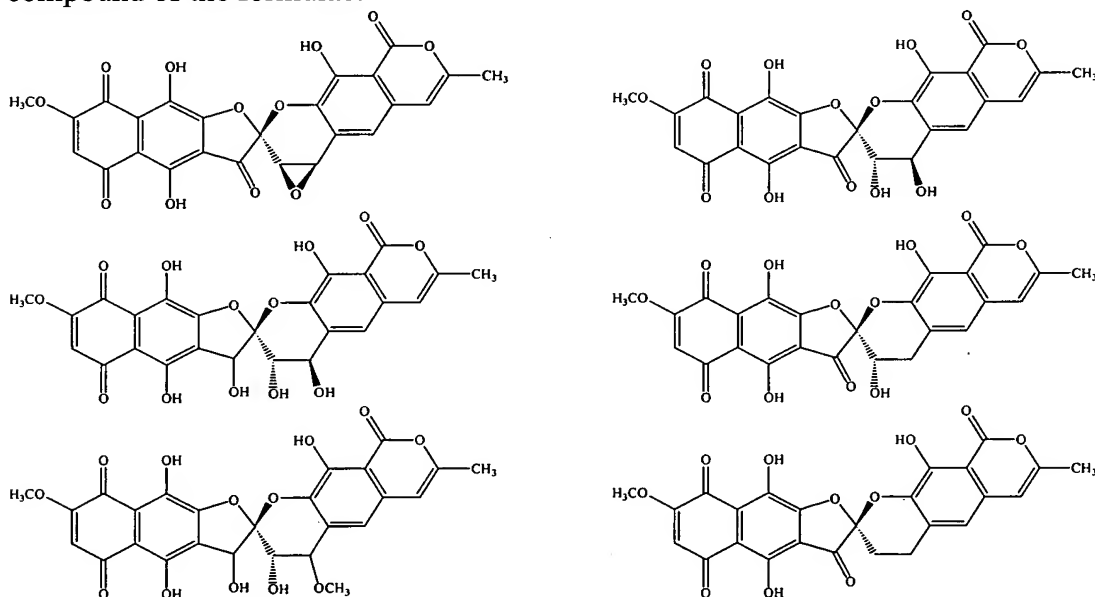
, or pharmaceutically acceptable salts, ester, or prodrugs thereof.

25. The method of claims 1, wherein the fredericamycin A compound has Formula VIII:



, or pharmaceutically acceptable salts, ester, or prodrugs thereof.

26. The method of claim 1, wherein the fredericamycin A compound is a compound of the formulae:



or pharmaceutically acceptable salts, prodrugs, and esters thereof.

27. The method of claim 1, wherein the fredericamycin A compound is a griseorhodin, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

28. A method for treating cyclin D1 overexpression in a subject comprising administering to a subject an effective amount of a fredericamycin A compound such that cyclin D1 overexpression is treated.

29. The method of claim 28, wherein the cyclin D1 overexpression results in neoplastic transformation.

5 30. The method of claim 28, wherein the cyclin D1 overexpression results in tumor growth.

31. The method of claim 28, wherein the treating comprises inhibiting tumor growth.

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32. The method of claim 28, wherein the treating comprises preventing the occurrence of tumor growth in the subject.

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33. The method of claim 28, wherein the treating comprises reducing the growth of a pre-existing tumor in the subject.

34. The method of claim 28, wherein the cyclin D1 overexpression results in colon cancer.

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35. The method of claim 28, wherein the cyclin D1 overexpression results in breast cancer.

36. The method of claim 28, wherein the cyclin D1 overexpression results in a sarcoma.

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37. The method of claim 28, wherein the cyclin D1 overexpression results in a malignant lymphoma.

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38. The method of claim 28, wherein cyclin D1 overexpression results in esophageal cancer.

39. The method of claim 28, wherein the cyclin D1 overexpression is caused by overexpression of Pin1.

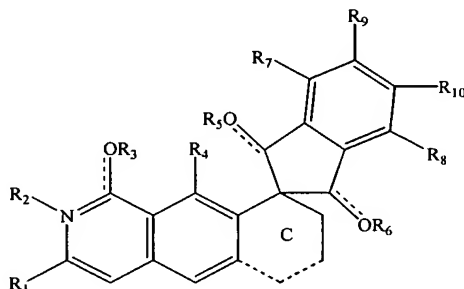
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40. The method of claim 28, wherein the cyclin D1 overexpression is caused by DNA damage.

41. The method of claim 28, wherein the cyclin D1 overexpression is caused by an oncogenic protein.

42. The method of claim 28, wherein cyclin D1 overexpression is caused by Ha-Ras.

43. The method of claim 28, wherein the fredericamycin A compound has Formula IX

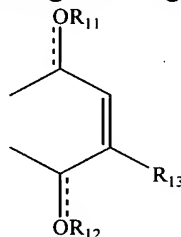


10 wherein the dotted lines around C indicate that C may be a 5 or 6 membered ring;  
wherein the dotted lines not around C indicate optional double bonds;

R<sub>1</sub> is alkyl, alkenyl, alkanoyl, alknyl;

R<sub>2</sub> is hydrogen or alkyl;

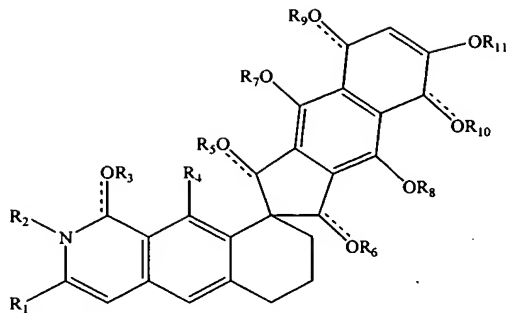
R<sub>9</sub> and R<sub>10</sub> are both hydrogen or together form a ring having the structure



15 R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>11</sub>, and R<sub>12</sub> are independently hydrogen, alkyl, alkanoyl, or nothing; and R<sub>4</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>13</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxy carbonyl, alkyl carbonyl, alkyl carbonyloxy, alkoxy carbonyloxy, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

20 44. The method of claim 28, wherein the fredericamycin A compound is fredericamycin A, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

25 45. The method of claim 28, wherein the fredericamycin A compound has Formula III



wherein the dotted lines indicate optional double bonds;

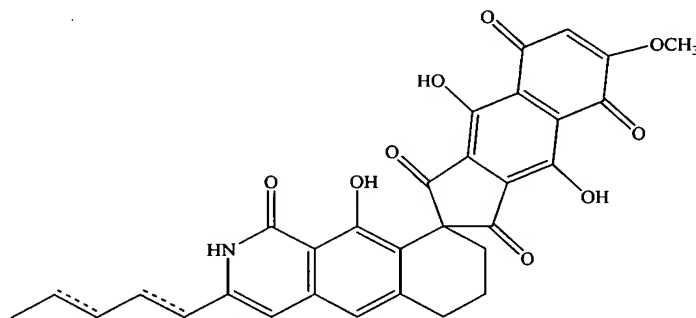
R<sub>1</sub> is alkyl having from 1 to 8 carbon atoms, alkenyl having from 2 to 8 carbon atoms, alkanoyl, or alkynyl having from 2 to 8 carbon atoms

5 R<sub>2</sub> is hydrogen or alkyl having from 1 to 8 carbon atoms;

R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>9</sub>, and R<sub>10</sub> are independently hydrogen, alkyl having from 1 to 8 carbon atoms, alkanoyl, or nothing; and

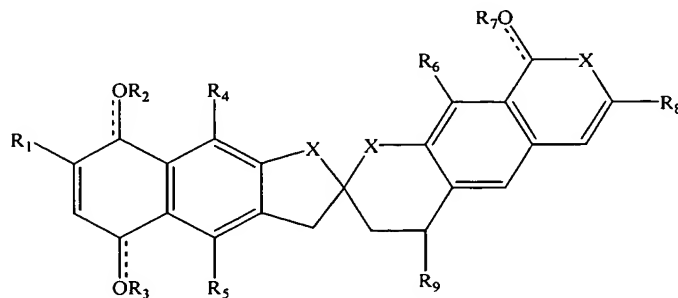
10 R<sub>4</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>11</sub> are independently hydrogen, alkyl having from 1 to 8 carbon atoms, or alkanoyl, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

46. The method of claim 28, wherein the fredericamycin A compound has Formula IV



15 wherein the dotted lines indicate optional double bonds, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

47. The method of claim 28, wherein the fredericamycin A compound has Formula VI



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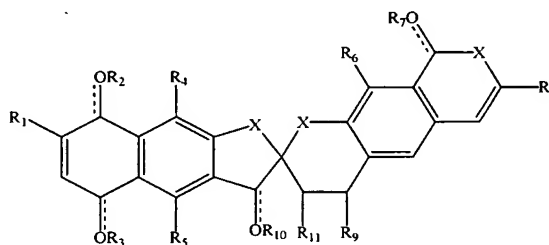
wherein the dotted lines indicate optional double bonds;

X is N, O, S, or C;

R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, and R<sub>9</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxyacetyl, alkylcarbonyl, alkylcarbonyloxy, alkoxyacetyl; and

R<sub>2</sub>, R<sub>3</sub>, and R<sub>7</sub> are independently hydrogen, alkyl, alkanoyl, or nothing, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

48. The method of claim 28, wherein the fredericamycin A compound has Formula XI



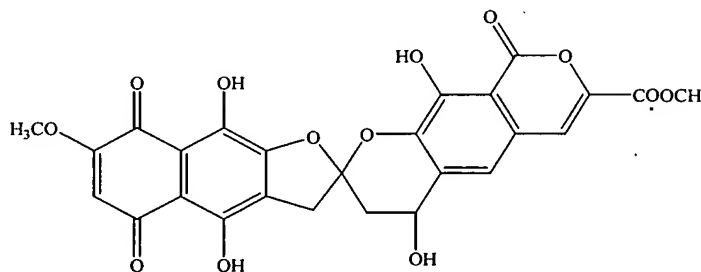
wherein the dotted lines indicate optional double bonds;

X is N, O, S, or C;

- R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>11</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxyacetyl, alkylcarbonyl, alkylcarbonyloxy, or alkoxyacetyl; or R<sub>9</sub> and R<sub>11</sub> taken together form an epoxide ring; and

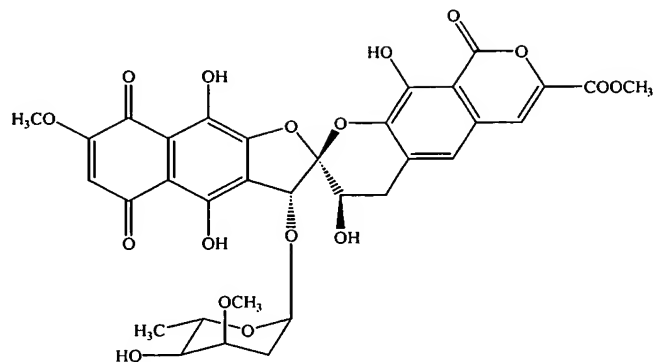
R<sub>2</sub>, R<sub>3</sub>, R<sub>7</sub>, and R<sub>10</sub> are independently hydrogen, alkyl, alkanoyl, or nothing, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

49. The method of claim 28, wherein the fredericamycin A compound has Formula VII



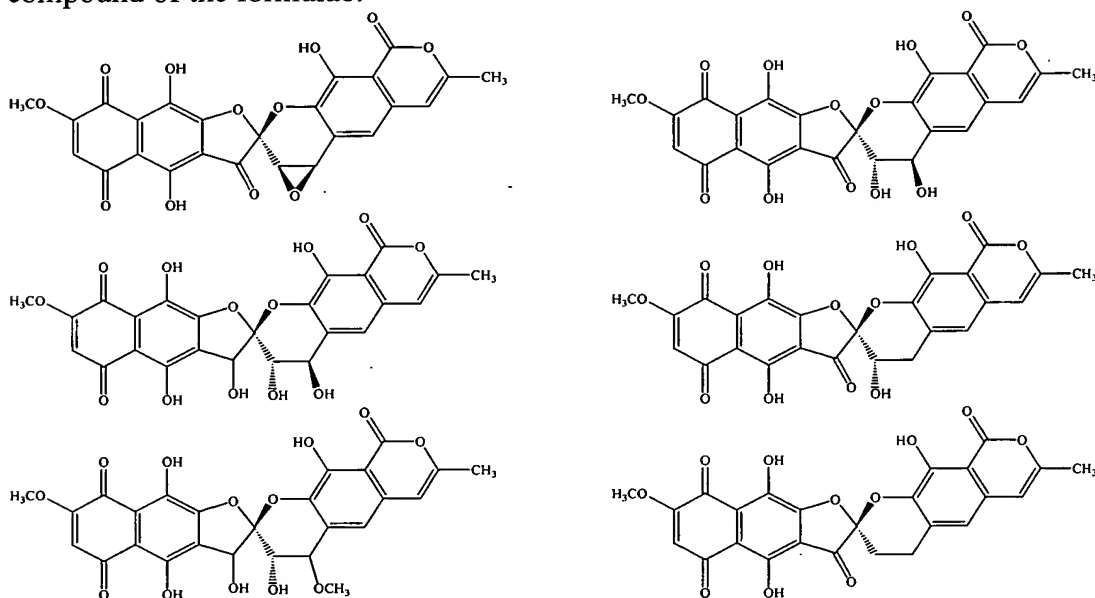
or pharmaceutically acceptable salts, prodrugs, and esters thereof.

50. The method of claim 28, wherein the fredericamycin A compound has Formula VIII



or pharmaceutically acceptable salts, prodrugs, and esters thereof.

51. The method of claim 28, wherein the fredericamycin A compound is a compound of the formulae:

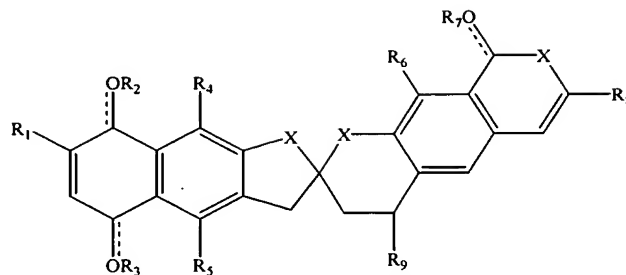


or pharmaceutically acceptable salts, prodrugs, and esters thereof.

52. The method of claim 28, wherein the fredericamycin A compound is a griseorhodin, or a pharmaceutically acceptable salt, prodrug or ester thereof.

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53. A method for treating tumor growth in a subject comprising administering to a subject an effective amount of a fredericamycin A compound having Formula VI



wherein the dotted lines indicate optional double bonds;

X is N, O, S, or C;

R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, and R<sub>9</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxycarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy; and

R<sub>2</sub>, R<sub>3</sub>, and R<sub>7</sub> are independently hydrogen, alkyl, alkanoyl, or nothing, or pharmaceutically acceptable salts, prodrugs, and esters thereof; such that the tumor growth is treated.

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54. The method of claim 53, wherein the treating comprises inhibiting tumor growth.

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55. The method of claim 53, wherein the treating comprises preventing the occurrence of tumor growth in the subject.

56. The method of claim 53, wherein the treating comprises reducing the growth of a pre-existing tumor in the subject.

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57. The method of claim 53, wherein the tumor growth is colon cancer.

58. The method of claim 53, wherein the tumor growth is breast cancer.

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59. The method of claim 53, wherein the tumor growth is a sarcoma.

60. The method of claim 53, wherein the tumor growth is a malignant lymphoma.

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61. The method of claim 53, wherein the tumor growth is esophageal cancer.

62. The method of claim 53, wherein the tumor growth is caused by overexpression of Pin1.

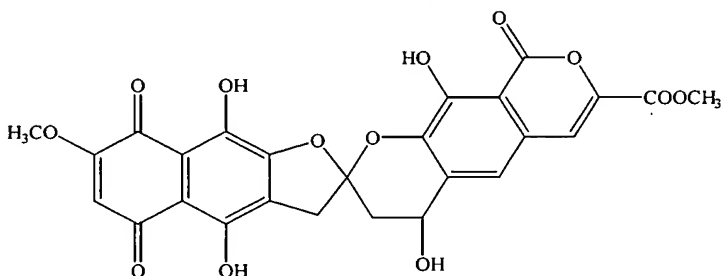
63. The method of claim 53, wherein the tumor growth is caused by DNA damage.

5 64. The method of claim 53, wherein the tumor growth is caused by an oncogenic protein.

65. The method of claim 53, wherein the tumor growth is caused by Ha-Ras.

10 66. The method of claim 53, wherein the tumor growth is caused by loss of Brcal or a mutation of Brcal.

67. The method of claim 53, wherein the fredericamycin A compound has Formula VII:



15 68. The method of claim 53, wherein the fredericamycin A compound is a griseorhodin, or a pharmaceutically acceptable salt, prodrug, or ester thereof.

20 69. A packaged Pin1-associated state treatment, comprising a fredericamycin A compound packaged with instructions for using an effective amount of the fredericamycin A compound to treat a Pin1-associated state.

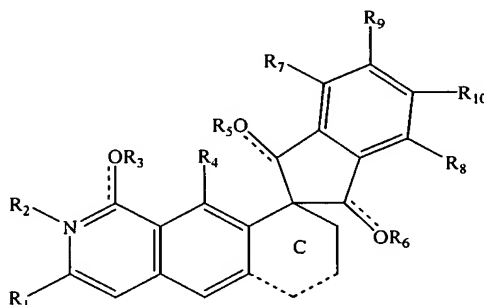
25 70. A packaged cyclin D1 overexpression treatment, comprising a fredericamycin A compound packaged with instructions for using an effective amount of the fredericamycin A compound to treat cyclin D1 overexpression.

30 71. A packaged cancer treatment, comprising a fredericamycin A compound packaged with instructions for using an effective amount of the fredericamycin A compound to treat cancer.

72. A method for treating a Pin1-associated state in a subject comprising

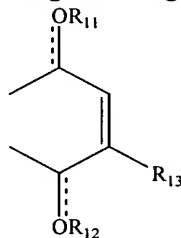
administering to a subject an effective amount of a combination of a fredericamycin A compound and a hyperplastic inhibitory agent such that the Pin1-associated state is treated.

- 5 73. The method of claim 72, wherein the fredericamycin A compound has Formula IX



wherein the dotted lines around C indicate that C may be a 5 or 6 membered ring;  
wherein the dotted lines not around C indicate optional double bonds;

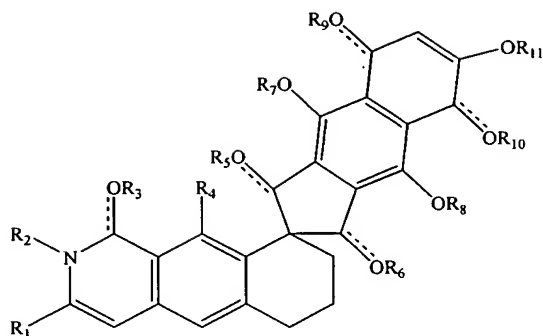
- 10 R<sub>1</sub> is alkyl, alkenyl, alkanoyl, alkenyl;  
R<sub>2</sub> is hydrogen or alkyl;  
R<sub>9</sub> and R<sub>10</sub> are both hydrogen or together form a ring having the structure



- 15 R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>11</sub>, and R<sub>12</sub> are independently hydrogen, alkyl, alkanoyl, or nothing; and R<sub>4</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>13</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxy carbonyl, alkyl carbonyl, alkyl carbonyloxy, alkoxy carbonyloxy, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

- 20 74. The method of claim 72, wherein the fredericamycin A compound is fredericamycin A, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

75. The method of claim 72, wherein the fredericamycin A compound has Formula III:



wherein the dotted lines indicate optional double bonds;

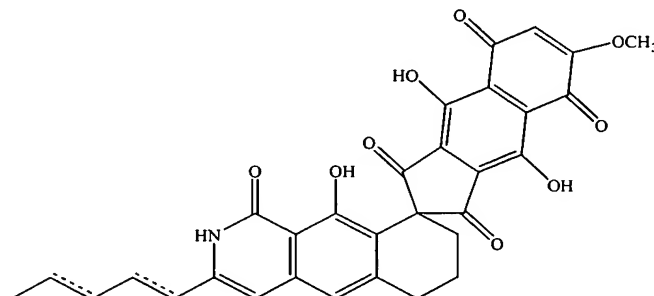
R<sub>1</sub> is alkyl having from 1 to 8 carbon atoms, alkenyl having from 2 to 8 carbon atoms, alkanoyl, or alkynyl having from 2 to 8 carbon atoms

5 R<sub>2</sub> is hydrogen or alkyl having from 1 to 8 carbon atoms;

R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>9</sub>, and R<sub>10</sub> are independently hydrogen, alkyl having from 1 to 8 carbon atoms, alkanoyl, or nothing; and

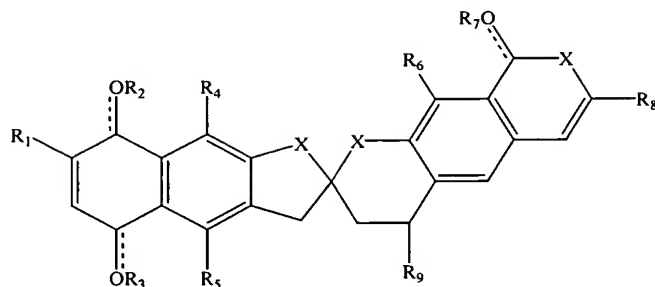
10 R<sub>4</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>11</sub> are independently hydrogen, alkyl having from 1 to 8 carbon atoms, or alkanoyl, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

76. The method of claim 72, wherein the fredericamycin A compound has Formula IV:



15 wherein the dotted lines indicate optional double bonds, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

20 77. The method of claim 72, wherein the fredericamycin A compound has Formula VI:



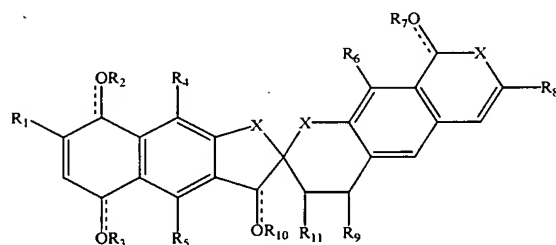
wherein the dotted lines indicate optional double bonds;

X is N, O, S, or C;

R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, and R<sub>9</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxy carbonyl, alkyl carbonyl, alkyl carbonyloxy, alkoxy carbonyloxy; and

R<sub>2</sub>, R<sub>3</sub>, and R<sub>7</sub> are independently hydrogen, alkyl, alkanoyl, or nothing, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

78. The method of claim 72, wherein the fredericamycin A compound has Formula XI



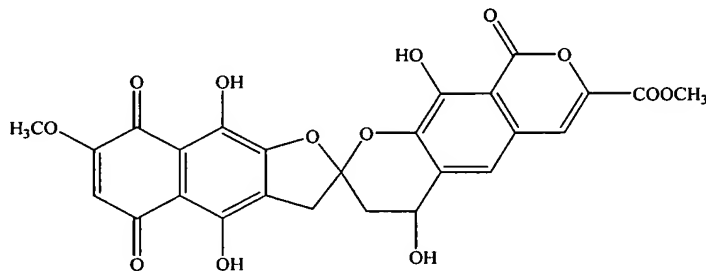
wherein the dotted lines indicate optional double bonds;

X is N, O, S, or C;

R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>11</sub> are independently hydrogen, alkyl, hydroxyl, alkoxy, alkanoyl, alkoxy carbonyl, alkyl carbonyl, alkyl carbonyloxy, or alkoxy carbonyloxy, or R<sub>9</sub> and R<sub>11</sub> taken together form an epoxide ring; and

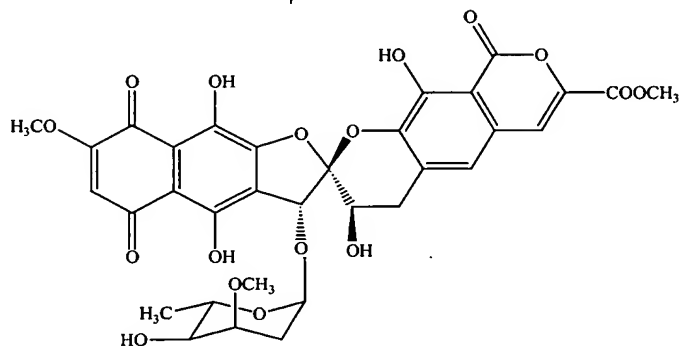
R<sub>2</sub>, R<sub>3</sub>, R<sub>7</sub>, and R<sub>10</sub> are independently hydrogen, alkyl, alkanoyl, or nothing, or pharmaceutically acceptable salts, prodrugs, and esters thereof.

79. The method of claim 72, wherein the fredericamycin A compound has Formula VII



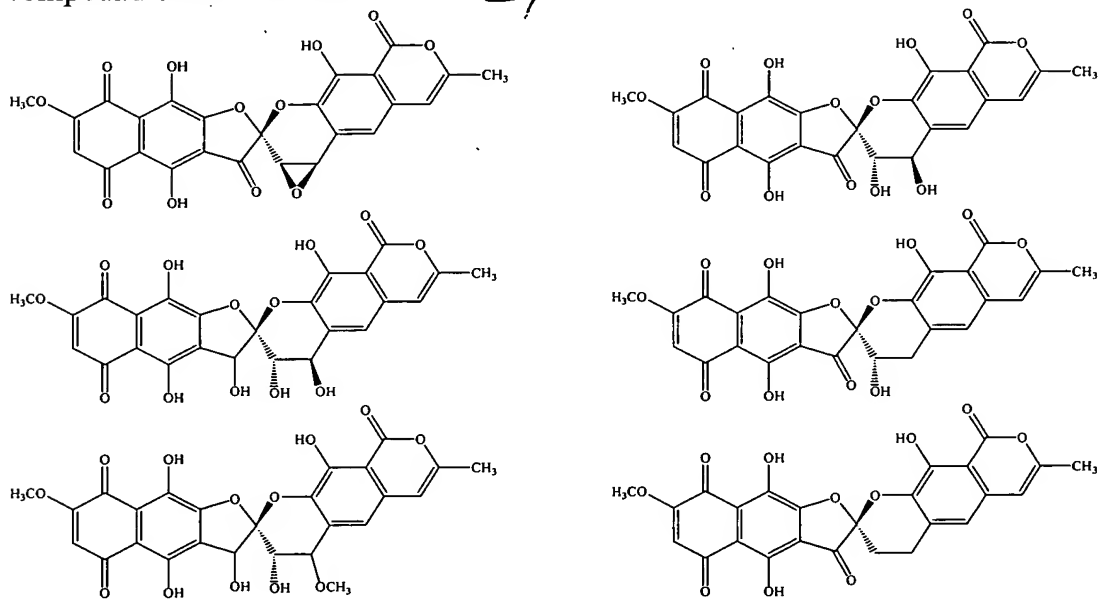
or pharmaceutically acceptable salts, prodrugs, and esters thereof.

80. The method of claim 72, wherein the fredericamycin A compound has Formula VIII:



or pharmaceutically acceptable salts, prodrugs and esters thereof.

81. The method of claim 72, wherein the fredericamycin A compound is a compound of the formulae:



or pharmaceutically acceptable salts, prodrugs, and esters thereof.

82. The method of claim 72, wherein the fredericamycin A compound is a griseorhodin.

83. The method of claim 72, wherein the hyperplastic inhibitory agent is tamoxifen.

84. The method of claim 72, wherein the hyperplastic inhibitory agent is



paclitaxel.

85. The method of claim 72, wherein the hyperplastic inhibitory agent is docetaxel.

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86. The method of claim 72, wherein the hyperplastic inhibitory agent is interleukin-2.

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87. The method of claim 72, wherein the hyperplastic inhibitory agent is rituximab.

88. The method of claim 72, wherein the hyperplastic inhibitory agent is tretinoin.

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89. The method of claim 72, wherein the hyperplastic inhibitory agent methotrexate.

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90✓ A method for treating cancer in a subject comprising administering to a subject an effective amount of a combination of a fredericamycin A compound and a hyperplastic inhibitory agent such that the cancer is treated.

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91✓ A method for treating cyclin D1 overexpression in a subject comprising administering to a subject an effective amount of a combination of a fredericamycin A compound and a hyperplastic inhibitory agent such that the cyclin D1 overexpression is treated.